REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

By the foregoing amendment, claim 52 has been added. New independent claim 52 is drawn to a method for the treatment of multiple sclerosis comprising administering directly to the muscle cells of a patient in need of such treatment, an effective amount of naked DNA comprising a nucleic acid encoding human beta-interferon. Support for this claim can be found throughout the originally-filed application including, for instance, page 7, lines 34-35. No new matter has been added.

Turning now to the Official Action, the Examiner has rejected claims 24 and 46-51 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Triantaphyllopous et al. (*Gene Therapy*, 5:253-63 (1998)) in view of Youssef et al. (*J. Immunol.*, 161:3870-79 (1998)), Felgner et al. (U.S. Patent No. 5,580,859) and Lemieux et al. (U.S. Patent No. 6,359,054). This rejection is respectfully traversed.

It is well recognized that obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention unless there was some teaching, suggestion or incentive in the cited prior art which would have made such a combination appropriate. To draw on hindsight knowledge of the present inventor's disclosure, when the prior art does not contain or suggest that knowledge, is to use applicant's invention as a template for its own reconstruction -- an illogical and inappropriate process by which to determine patentability. Applicant's invention must be viewed not after the blueprint has been drawn by the inventor, but as it

would have been perceived in the state of the art that existed at the time the invention was made. *Sensonics Inc. v. Aerosonic Corp.*, 38 U.S.P.Q.2d 1551, 1554 (Fed. Cir. 1996). Here, absent the impermissible use of hindsight reconstruction, one of skill in the art would not have been motivated to use intramuscular injections for the treatment of multiple sclerosis. Rather, based on the teachings of the references cited by the Examiner, such references "teach away" from applicant's claimed invention.

Triantaphyllopous et al. describes the use of a plasmid comprising the IFNβ gene for the therapy of experimental automimmune encephalomyelitis ("EAE") in mice. In Triantaphyllopous et al. the plasmid is associated with lipofectin and is injected intracranially (see page 257, 1st column, 1st full paragraph).

Youssef et al. teaches that MIP1α and MIP1 are involved in the initiation of EAE (see page 3877, 2nd column, lines 1-9). Youssef et al. also teaches that vaccination against MIP1α and MIP1, by direct injection into muscle cells of a naked DNA encoding these proteins, leads to the production of anti- MIP1α and anti-MIP1 immune responses which protect injected rats from EAE (see abstract).

According to the Examiner, Felgner et al. teaches the direct administration of naked DNA molecules to tissues for providing a therapeutic protein for treating diseases and for vaccination.

Lemieux et al. discloses that the intramuscular injection of naked DNA leads to the expression of the injected gene. However, Lemieux et al. stresses that this application is very limited because the expression of the gene is low (see column 1, lines 33-35). Therefore, Lemieux et al. proposes to use compositions comprising polynucleotides such as RNA, DNA or their derivatives, and block copolymers

(column 2, lines 61-63). Moreover, Lemieux et al. does not disclose the use of intramuscular injections of DNA for the treatment of immune diseases such as multiple sclerosis.

Considering the references cited by the Examiner as a whole, one skilled in the art would have thought that:

- the production of IFNβ in the central nervous system leads to a protection against EAE (see Triantaphyllopous);

- the injection of a naked DNA coding for a protein, into muscle cells, lead to an immune response against this protein (see Felgner and Youssef); and

- the intramuscular injection of a naked DNA leads to a low expression of a gene (see Lemieux et al.).

Thus, one skilled in the art, would have thought that the intramuscular injection of a naked nucleic acid encoding IFNβ leads to the production of an immune response against IFNβ. However, this immune response is known to induce the neutralization of the protein in the central nervous system (see Youssef et al., page 3877, 2nd column, lines 49-54) which is contradictory with the need to increase the production of IFNβ disclosed by Triantaphyllopous.

These conclusions are corroborated by Croxford et al. which discloses that a single i.m. injection of 100 µg of cytokine DNA (i.e. naked DNA encoding IFNβ) fails to ameliorate the disease severity or the onset of disease (see last paragraph, 2nd column, page 5182 and Table I, page 5183). This is also corroborated by Lemieux et al. which teaches to use DNA with block copolymer instead of naked DNA in order to have a sufficient expression of the gene.

As such, one skilled in the art would not have been motivated to use intramuscular injections for the treatment of multiple sclerosis. Rather, based on the teachings combined by the Examiner, the skilled artisan would have been taught away from using intramuscular injections for the treatment of multiple sclerosis.

Because there is no motivation to combine the references cited by the Examiner to arrive at the present invention with a reasonable expectation of success, applicant submits that the cited references do not and indeed cannot render the claimed invention obvious. Thus, for at least these reasons, applicant respectfully requests withdrawal of the rejection of claims 24 and 46-51 under 35 U.S.C. § 103(a).

It is noted that dependent claim 43, which specifies the beta-interferon as being human beta-interferon, was not rejected (or even objected to) by the Examiner. New independent claim 52 is similarly directed to administering, directly to the muscle cells of a patient, an effective amount of naked DNA comprising a nucleic acid encoding human beta-interferon. Therefore, just like claim 43, new independent claim 52 should be free from rejections or objections by the Examiner.

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this Amendment and Reply, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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